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Original Article

Mechanism of PPARα agonist in alopecia areata

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Abstract: Objective: To investigate the involvement and mechanisms of PPARα agonists in alopecia areata (AA). Methods: AA models were established using skin grafting, adoptive T-cell transfer, and TCR retrograde T-cell transfer methods. Relative PPARα expression levels in C3H/HeJ AA mice and AA patients were evaluated using qPCR and immunohistochemistry (IHC). Hair changes in mice following treatment were documented photographically, while immunofluorescence staining was employed to assess inflammatory factor dynamics in the skin. Additionally, ELISA and flow cytometry were used to analyze AA-related immune factors and cell populations in treated mice. Results: PPARα agonists demonstrated protective effects in C3H/HeJ skin graft AA models and TCR transgenic AA mice, promoting early reversal of AA. They effectively inhibited T effector cell function and exerted immunomodulatory effects. Conclusion: The PPARα signaling pathway plays a key role in AA pathogenesis. PPARα agonists show therapeutic potential for AA as an inflammatory condition.

Keywords: PPARα agonist, PPARα signal pathway, alopecia areata, mechanism, immunomodulation

Introduction

Alopecia areata (AA) is a common autoimmune skin disease characterized by round or oval patches of hair loss without scarring, affecting the scalp or other hair-bearing areas. It is estimated to impact 1-2% of the general population, with a lifetime risk of approximately 1.7% [1, 2]. Based on the extent and severity of hair loss, AA is classified into three main forms: patchy AA (AAP), the most common, marked by localized hair loss on the scalp or other areas such as the beard; alopecia totalis (AT), which involves complete scalp hair loss; and alopecia universalis (AU), the most severe form, characterized by widespread hair loss across the body [3, 4].

Immune factors are central to the development of AA [1]. Histological analyses have shown significant infiltration of immune cells, including CD4+ and CD8+ T cells, natural killer (NK) cells, and macrophages, around affected hair follicles. Genome-wide association studies (GWAS) have identified loci linked to innate and adaptive immune responses, including ULBP3 and ULBP6, which encode ligands for NKG2D [2]. These ligands target CD8+NKG2D+ T cells, contributing to AA progression [7]. Cytotoxic CD8+NKG2D+ T cells producing IFN-γ are pivotal in AA pathology. Blocking IFN-γ through antibody-mediated approaches or inhibiting the Janus kinase (JAK) pathway has been shown to prevent AA by mitigating the IFN signature [8]. Additionally, cytokines such as TH1, TH2, IL-23, and IL-9/TH9 have been implicated in AA pathogenesis, offering potential targets for therapy [9]. Despite these advances, the precise mechanisms of AA remain unclear, and immune-related biomarkers for assessing severity and guiding treatment are lacking.

Alopecia areata is now recognized as a T cell-mediated autoimmune disease triggered by the breakdown of immune privilege in hair follicles. The development and cycling of hair follicles depend on the interplay of signaling pathways, including Wnt, BMP, Shh, Notch, and mTOR,

between epithelial and mesenchymal cells [3]. AA often coexists with autoimmune and inflammatory diseases, significantly affecting patients' quality of life [12]. Traditional treatments include glucocorticoids, minoxidil, contact immunotherapy, and immunosuppressants like methotrexate and cyclosporine [13]. However, glucocorticoids, while effective, can cause adverse effects such as capillary dilation, obesity, blood pressure and glucose fluctuations, and hypothalamic-pituitary axis suppression with long-term use [14]. Minoxidil, particularly at 5%, is effective for plaque-type AA but often requires combination therapy for complete hair regrowth [15].

To minimize the side effects of conventional therapies, novel agents such as JAK inhibitors (JAKi), biologics, and platelet-rich plasma have been investigated [16, 17]. JAK inhibitors target the JAK-STAT signaling pathway, which plays a role in various autoimmune and skin diseases, including psoriasis, atopic dermatitis, pemphigus vulgaris, and vitiligo [18, 19]. JAK inhibitors, such as baricitinib, have been officially approved for treating pemphigus vulgaris and promote hair follicle growth by suppressing inflammatory cytokines [20, 21]. These agents mark a new era of targeted therapy for AA. Although peroxisome proliferator-activated receptor (PPAR) α agonists have been studied for their roles in regulating immune responses, keratinocyte differentiation, lipid synthesis, and skin inflammation, their impact on AA remains poorly understood [22-24]. This study aims to investigate the role and mechanisms of PPARα agonists in AA, exploring their therapeutic potential in this autoimmune condition.

Materials and methods

Mice and the AA mouse model

All mice, including male C3H/HeJ mice and male B6.129S7-Rag1tm1Ma/J (Rag1-/-B6) mice, aged 6-8 weeks and weighing approximately 20 g, were obtained from The First Hospital of Hebei Medical University. At the end of the experiments, mice were euthanized by cervical dislocation. The mice were housed in specific pathogen-free (SPF) environments, and all experiments were conducted in compliance with institutional guidelines approved by the Institutional Animal Care and Use Committee of The First Hospital of Hebei Medical University.

The C3H/HeJ AA mouse model was established using skin grafting and adoptive T-cell transfer from subdermal lymph nodes (SDLNs) as described previously [25]. Briefly, mice were randomized into control, model, and treatment groups, each consisting of six animals. Hair regrowth in the mice was photographed and recorded weekly for analysis.

Skin transplantation model: Skin (2 cm in diameter) from C3H/HeJ mice that spontaneously developed AA was transplanted onto healthy C3H/HeJ mice.

Cell transplantation model: CD8+ T cells isolated from the SDLNs of C3H/HeJ AA mice were directly injected into recipient mice. This approach avoids surgical procedures and facilitates the generation of large numbers of AA mice for research purposes [26].

1MOG244.1 TCR Retrograde Mice: The modeling process followed established protocols.

Rag1-/-B6 mice were treated with 5-fluorouracil (Sigma-Aldrich). After 3 days, bone marrow cells were collected and cultured for 24 hours at 37°C with 5% CO_2 in Dulbecco's Modified Eagle Medium (DMEM) supplemented with recombinant murine IL-3 (20 ng/ml, PeproTech), recombinant human IL-6 (50 ng/ml, PeproTech), recombinant murine stem cell factor (SCF) (50 ng/ml, PeproTech), 20% fetal calf serum (FCS), and polybrene (6 μg/ml, Sigma-Aldrich). Bone marrow cells were infected with TCR-expressing retroviruses using spin-transduction (1,000 g, 37°C, 60 minutes) and further cultured for 48 hours in DMEM. Transduced bone marrow cells were injected into RAG1-/- C57BL/6 mice via the orbital vein at a ratio of one recipient mouse per two bone marrow donors.

Samples from patients with AA

The study included 8 healthy individuals without skin disease and 8 patients with AA hospitalized at the First Hospital of Hebei Medical University between January 2022 and June 2023. Tissue samples were collected for RNA extraction and subsequent experiments. All study protocols complied with the Declaration of Helsinki and were approved by the Ethics Committee of The First Hospital of Hebei Medical University. Informed consent was obtained from all participants after explaining the study's purpose and procedures.

In vivo treatment

The PPARα inhibitor (GW6471; HY-15372, MCE, USA) and agonist (Pirinixic acid; HY-16995, MCE, USA) were initially dissolved in a small volume of dimethyl sulfoxide (DMSO) and subsequently diluted with polyethylene glycol 300. These solutions were administered to C3H/HeJ AA mice via intraperitoneal injections twice weekly at dosages of 20 mg/kg body weight (inhibitor) and 10 mg/kg body weight (agonist). The injections commenced on the day of transplantation in the C3H/HeJ model or adoptive T-cell transfer in the retrotransposon TCR C57-BL/6 model. Hair regrowth and shedding were monitored weekly, photographed, and quantified using established methods. At the conclusion of the treatment, mouse skin and SDLN tissues were collected for qPCR, immunofluorescence, and immunohistochemistry analyses.

Flow cytometric analysis

To prepare single-cell suspensions from skin tissues, samples were cleaned, degreased, and digested with 0.25% trypsin for 20 minutes. Dermal tissues were further digested with collagenase I (Yeasen, China) and DNase (D70-73, Beyotime, China), ground or finely cut, filtered, and washed with PBS three times before staining. Fluorescently labeled antibodies for staining were procured from Invitrogen. SDLNs were ground, filtered, washed, and stained in a similar manner. Dead cells were excluded using LIVE/DEAD Fixable Blue, and non-specific antibody binding was blocked with TruStain FcX.

For surface labeling, cells were incubated directly with combinations of fluorescently coupled monoclonal antibodies for 30 minutes. For intracellular factor staining, cells were fixed, permeabilized, and then stained with the respective antibodies. The stained cells were analyzed on an LSRII flow cytometer (BD Biosciences), and data were processed using FlowJo software.

Quantitative real-time PCR

Total RNA was extracted from AA skin tissue and human scalp samples using Trizol reagent. The mRNA was reverse-transcribed into cDNA using SuperScript III Reverse Transcriptase (Thermo Fisher Scientific) and Oligo(dT)18 primers. Quantitative PCR was performed using the SYBR Green Amplification Kit (Thermo Fisher Scientific) in a QuantStudio 7 PCR detection system (Thermo Fisher Scientific).

Cell stimulation and ELISA spot

Purified CD4+ or CD8+ T cells were cultured in RPMI 1640 medium supplemented with 10% fetal serum, 4 mM GlutaMAX, 20 mM Hepes, 0.05 mM 2-mercaptoethanol, and penicillin-streptomycin. T cells were stimulated with Dynabeads mouse T-activator CD3/CD28 (Thermo Fisher Scientific) at a bead-to-cell ratio of 2:1. Interferon-gamma (IFN-γ) or interleukin-2 (IL-2) production was measured using an ELISA kit (BioLegend).

Immunofluorescence staining

Mouse skin tissues were fixed in acetone, dehydrated, and embedded in OCT compound for frozen sections. After blocking with 5% goat serum for 1 hour, sections were incubated overnight at 4°C with anti-CD8, anti-MHC-I, or anti-MHC-II monoclonal antibodies. Fluorescently conjugated secondary antibodies and DAPI were used for staining. Images were captured using a laser scanning confocal microscope.

Immunohistochemistry staining

Mouse skin and human scalp tissues were fixed in 4% paraformaldehyde, dehydrated in graded ethanol and xylene, and embedded in paraffin. Tissue sections (6 μm) were deparaffinized, microwaved in PBS containing 10 mM Tris and 1 mM EDTA (pH 8.0) for antigen retrieval, and blocked with 5% donkey serum. Sections were incubated overnight at 4°C with anti-CD4, anti-CD8, and anti-PPARα (Abcam) antibodies. Secondary antibody complexes were detected with ImmPRESS HRP, followed by ImmPACT NovaRED peroxidase substrate (Vector Laboratories). Counterstaining was performed with Mayer's hematoxylin for 2 minutes and blued in Scott's tap solution. Images were captured under a fluorescence microscope.

Statistical analysis

All data were analyzed using GraphPad Prism software (GraphPad Software Inc.). Differences between the two groups were assessed using a two-tailed Student's t-test. Hair loss or regrowth curves were analyzed with the log-rank test. Comparisons across multiple groups were ma-

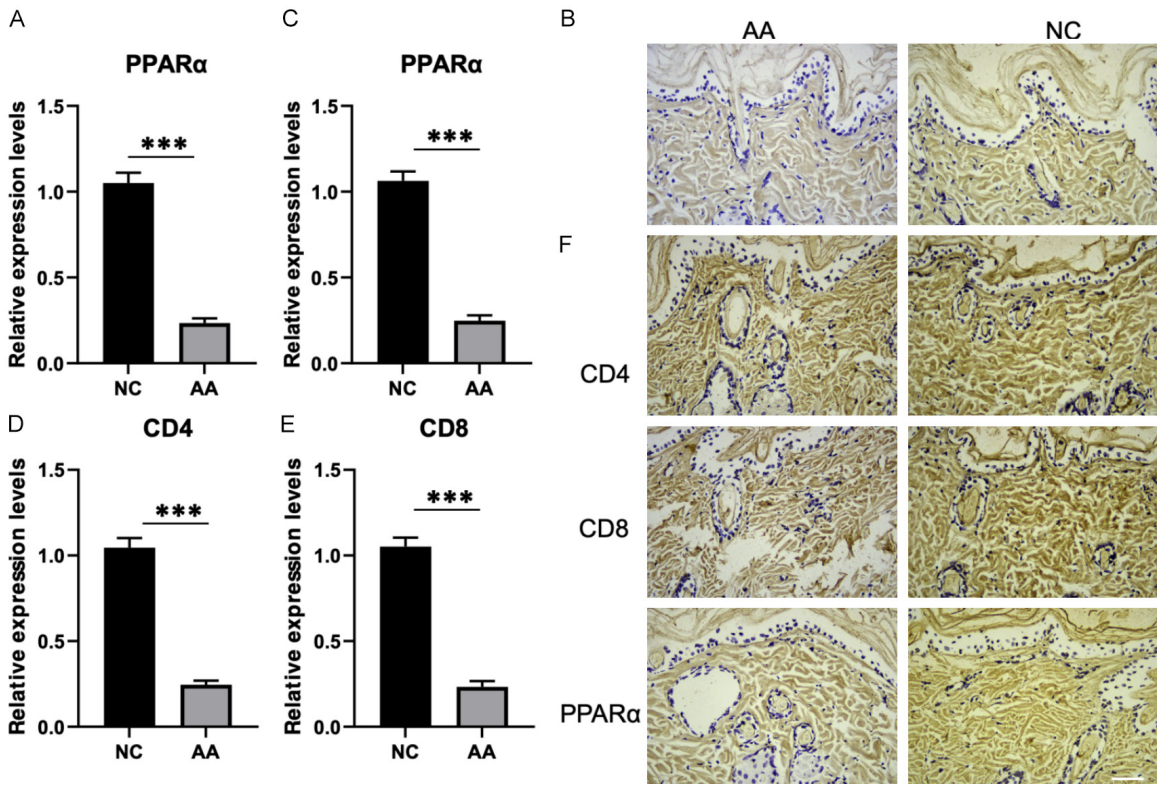

Figure 1. Increased PPARα pathway in alopecia areata (AA) lesional skin. A. Polymerase chain reaction (qPCR) analysis of the relative expression of PPARα in the skin of normal and C3H/HeJ AA mice. B. Representative immunohistochemical (IHC) images of PPARα in skin sections of normal and C3H/HeJ AA mice. C-E. Relative expression levels of PPARα, CD4 and CD8 in the skin of alopecia areata patients and normal subjects. F. IHC analysis of PPARα, CD4 and CD8. NC, negative control. Scale bar, 50 μm, ***P<0.001 (one-way ANOVA).

de using one-way ANOVA. Results are presented as mean ± SEM, with significance levels denoted as *P≤0.05, **P<0.01, ***P<0.001.

Results

Decreased expression of PPARα pathway activity in lesional skin affected by AA

PPARα is expressed in both dermal and epithelial cells of human hair follicles and positively influences the survival of cultured human hair follicles [27]. However, its specific role in AA remains unclear. Through qPCR and immunohistochemistry analyses of skin samples from C3H/HeJ AA mice and AA patients, we observed significantly lower PPARα expression in the lesional skin of C3H AA mice compared to non-alopecic controls (C3H NC) (**Figure 1A**). Similarly, the expression levels of PPARα, CD4+ T cells, and CD8+ T cells were markedly reduced in scalp tissues of AA patients compared to normal controls (**Figure 1C-E**). Immunohistochemistry corroborated these findings, showing low expression of PPARα, CD4+ T cells, and CD8+ T cells in human AA skin biopsies (**Figure 1B**, **1F**).

PPARα inhibitors accelerate the progression of AA

AA is a T cell-mediated autoimmune disease driven by the breakdown of immune tolerance in hair follicles, with cytotoxic T lymphocytes (CTLs) playing a pivotal role. To investigate the effects of PPARα inhibition, we treated CD4+ and CD8+ T cells with a PPARα inhibitor. This treatment significantly increased the production of IFN-γ+CD4+ T cells and IFN-γ+CD8+ T cells (**Figure 2A**) and elevated cytotoxic mediators, such as granzymes (GZMs) and perforin-1 (PRF1), enhancing the cytotoxicity of CD8+ T cells (**Figure 2B**).

In vivo, C3H/HeJ AA mice treated with a PPARα inhibitor showed no suppression of hair loss after two weeks (**Figure 2C**, **2D**). Flow cytometry revealed that PPARα inhibitor-treated mice exhibited higher levels of IFN-γ+CD8+ T cells in

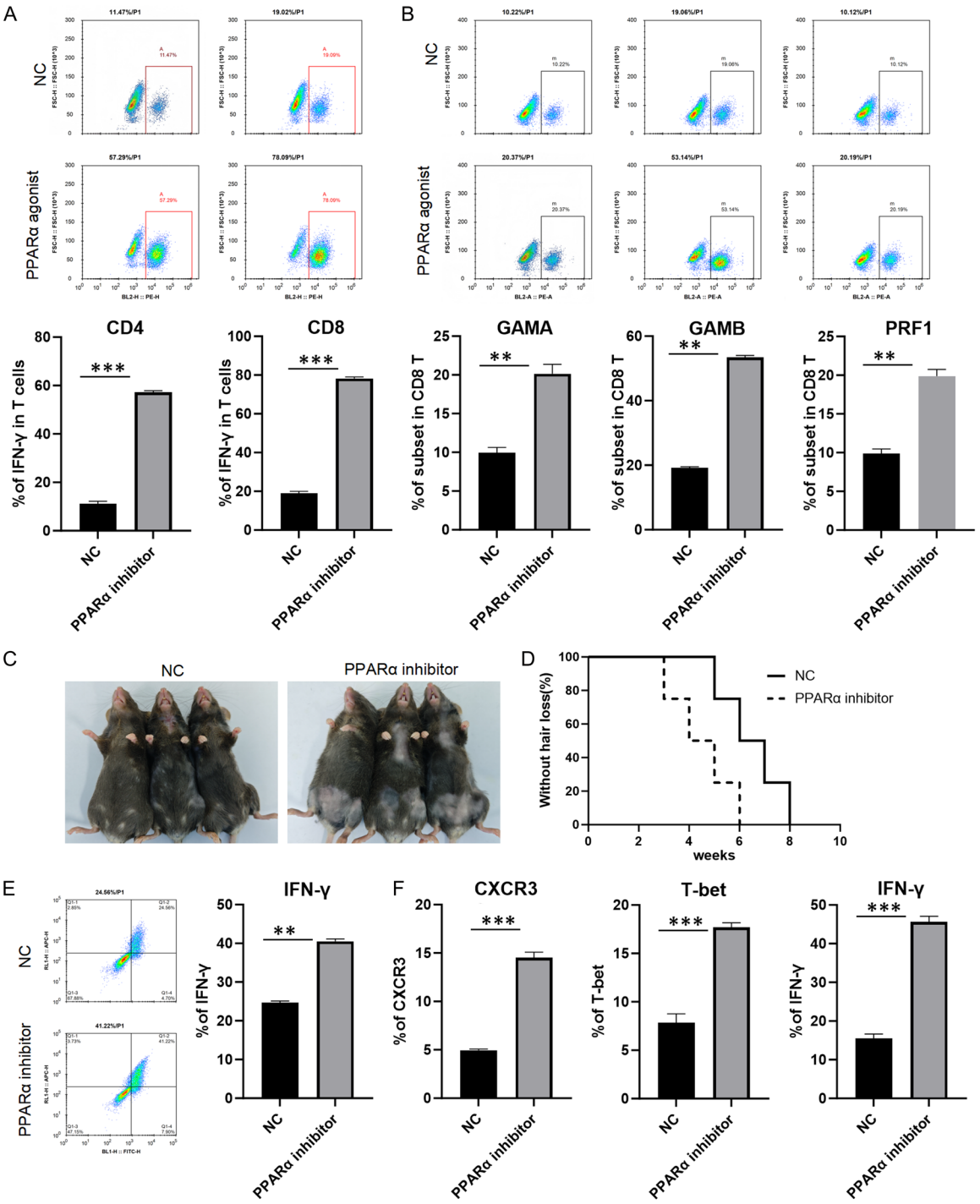

Figure 2. PPARα inhibitors accelerate the progression of AA. A. Flow cytograms and percentage plots of IFN-γ+CD4+ T cells and IFN-γ+CD8+ T cells after 4 days of PPARα inhibitor stimulation of initial CD4+ and CD8+ T cells. B. Flow cytograms and percentage plots of CD8+ T cells with GZMA, GZMB, or PRF1. The data, which represents the mean ± SD of three independent experiments, showed statistically significant differences (***P*<0.01, ****P*<0.001, unpaired Student's t-test). C and D. Hair pictures and frequency of hair shedding after PPARα inhibitor treatment of C3H/HeJ transplanted AA mice. E. Flow cytometric sorting and summary plots of IFN-γ+CD8+ T cells in the skin of the transplanted mice revealed distinct patterns. F. Summary plot of the percentage of CXCR3+CD8+ T cells, T-bet+CD8+ T cells, and IFN-γ+CD8+ T cells generated in SDLN. Data are expressed as mean ± SD of two independent experiments. NC, negative control. ***P*<0.01, ****P*<0.001 (one-way ANOVA).

skin tissues, promoting disease progression (**Figure 2E**). Furthermore, analysis of SDLNs indicated increased frequencies of CXCR3+ CD8+ T cells, T-bet+CD8+ T cells, and IFN-γ+ CD8+ T cells, along with elevated pro-inflammatory cytokines (**Figure 2F**). These findings indicate that PPARα inhibitors exacerbate AA by enhancing CTL-mediated immune responses.

PPARα agonists prevent the development of AA in C3H/HeJ mice

We next examined whether PPARα agonists could inhibit the onset of AA in C3H/HeJ skin graft mice. In the control group, hair loss began by the fourth week, whereas PPARα agonist-treated mice showed no signs of hair loss (**Figure 3A**, **3B**). Immunofluorescence staining revealed reduced expression of CD8, MHC I, and MHC II in the treated group (**Figure 3C**). Flow cytometry of skin tissues confirmed decreased numbers of CD45+ leukocytes, CD44+ CD62L-CD8+ T cells, NKG2D+CD8+ T cells, and IFN-γ+CD8+ T cells following PPARα agonist treatment (**Figure 3D**, **3E**).

PPARα agonists prevent the pathogenesis of T cell receptor transgenic AA mice

To establish the desired animal model, CD8+ T cells purified from 1MOG244 transgenic TCR B6 RAG1-/- mice were transferred into RAG1-/- C57BL/6 mice. The mice were then treated with either a PPARα agonist or a control, and their hair growth was monitored and quantified weekly. As shown in **Figure 4A**, **4B**, PPARα agonist treatment effectively prevented hair loss, whereas all control mice developed AA. Immunofluorescence staining revealed that PPARα agonist treatment significantly attenuated the expression of inflammatory markers, including CD8, MHC I, and MHC II, in the skin (**Figure 4C**). Similarly, flow cytometric analysis demonstrated that the frequencies of CD45+ leukocytes, CD44+CD62L-CD8+ T cells, NKG2D+CD8+ T cells, and IFN-γ+CD8+ T cells were markedly reduced in the PPARα agonists-treated group (**Figure 4D**). These results indicate that PPARα agonists effectively inhibit the development of AA in the C57BL/6 1MOG244 TCR mouse model.

PPARα agonists reverse early AA in C3H/HeJ mice

Following transplantation, C3H/HeJ mice typically exhibit hair loss between 5-7 weeks. At this stage, PPARα agonists were administered to evaluate their impact on early-stage AA in a clinically relevant context. After 8 weeks of treatment, the PPARα agonist group showed hair regrowth, whereas the control group experienced continued hair loss (**Figure 5A**, **5B**). The treated mice also displayed reduced skin inflammation, as evidenced by lower expression levels of CD8, MHC I, and MHC II (**Figure 5C**). Flow cytometric analysis of single-cell suspensions from skin tissue confirmed a notable reduction in CD45+ cells, total CD8+ T cells, and IFN-γ+CD8+ T cells in the treated group (**Figure 5D**). These findings suggest that PPARα agonists can suppress effector T cell activity, inhibit inflammatory responses, and potentially reverse AA.

PPARα agonists inhibit the immunoregulatory function of desmoplastic T effector cells

To further assess the immunomodulatory effects of PPARα agonists, levels of IFN-γ and IL-2 secreted by CD8+ T cells in SDLNs were measured using ELISA. As shown in **Figure 6A**, PPARα agonists significantly reduced the production of these pro-inflammatory cytokines. Previous studies demonstrated that transferring CD8+ T cells from SDLNs of C3H/HeJ AA mice into young C3H/HeJ recipients induces AA. However, in our study, PPARα agonist-treated mice showed no hair loss, even after receiving CD8+ T cells from isotype-treated donors. In contrast, control mice exhibited complete hair loss within 10 weeks, indicating that PPARα agonists effectively inhibit the function of alopecia effector T cells (**Figure 6B**, **6C**).

Flow cytometric analysis revealed a reduction in lymphocyte populations, including CD3+ T cells, CD4+ T cells, CD8+ T cells, and B cells, in SDLNs of PPARα agonist-treated mice (**Figure 6D**, **6E**). Moreover, these mice exhibited a significant increase in PD-1+ T cells, suggesting an enhanced regulatory T cell response (**Figure 6F**). Collectively, these findings indicate that PPARα agonists reduce the frequency and activity of alopecia effector T cells, thereby preventing hair loss and mitigating AA progression.

Discussion

AA is an autoimmune disorder characterized by various inflammatory responses [5]. Biologics and small-molecule drugs have been widely used to manage autoimmune inflammatory

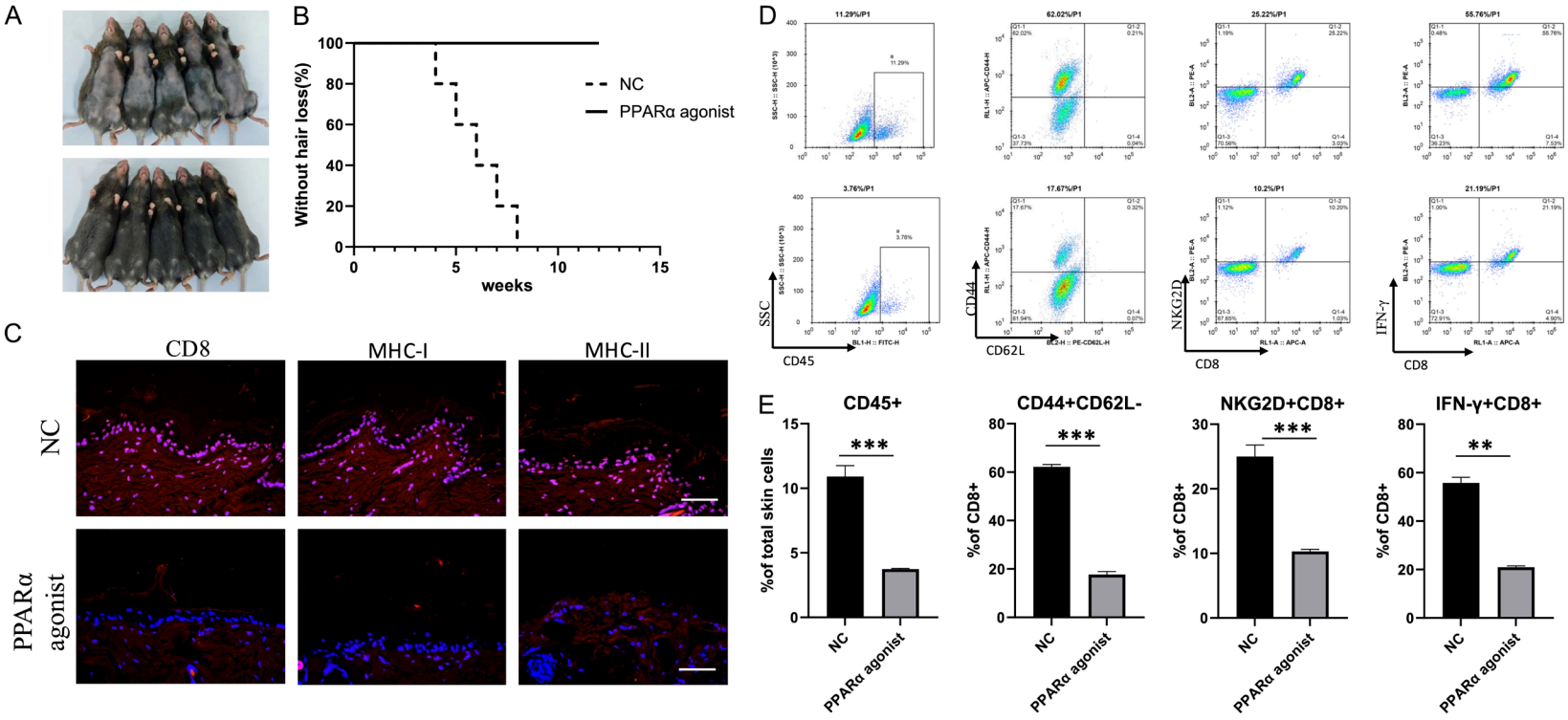

Figure 3. PPARα agonist treatment prevents AA. PPARα agonist treatment was given to C3H/HeJ transplanted mice for 4 weeks. A, B. Representative pictures and hair growth curves of PPARα agonist and control mice. C. Representative immunofluorescence images of skin sections from mice in different treatment groups stained with anti-CD8, anti-MHC class I or anti-MHC class II monoclonal antibodies, respectively. D, E. Flow cytometric analysis plots and percentage summary plots of CD45+ leukocytes, CD44+CD62L-CD8+ T cells, NKG2D+CD8+ T cells, and IFN-γCD8+ T cells in the skin of mice from different treatment groups. NC, negative control. AA, Alopecia areata. Scale bar, 50 μm. $^{**}P<0.01$, $^{***}P<0.001$ (one-way ANOVA).

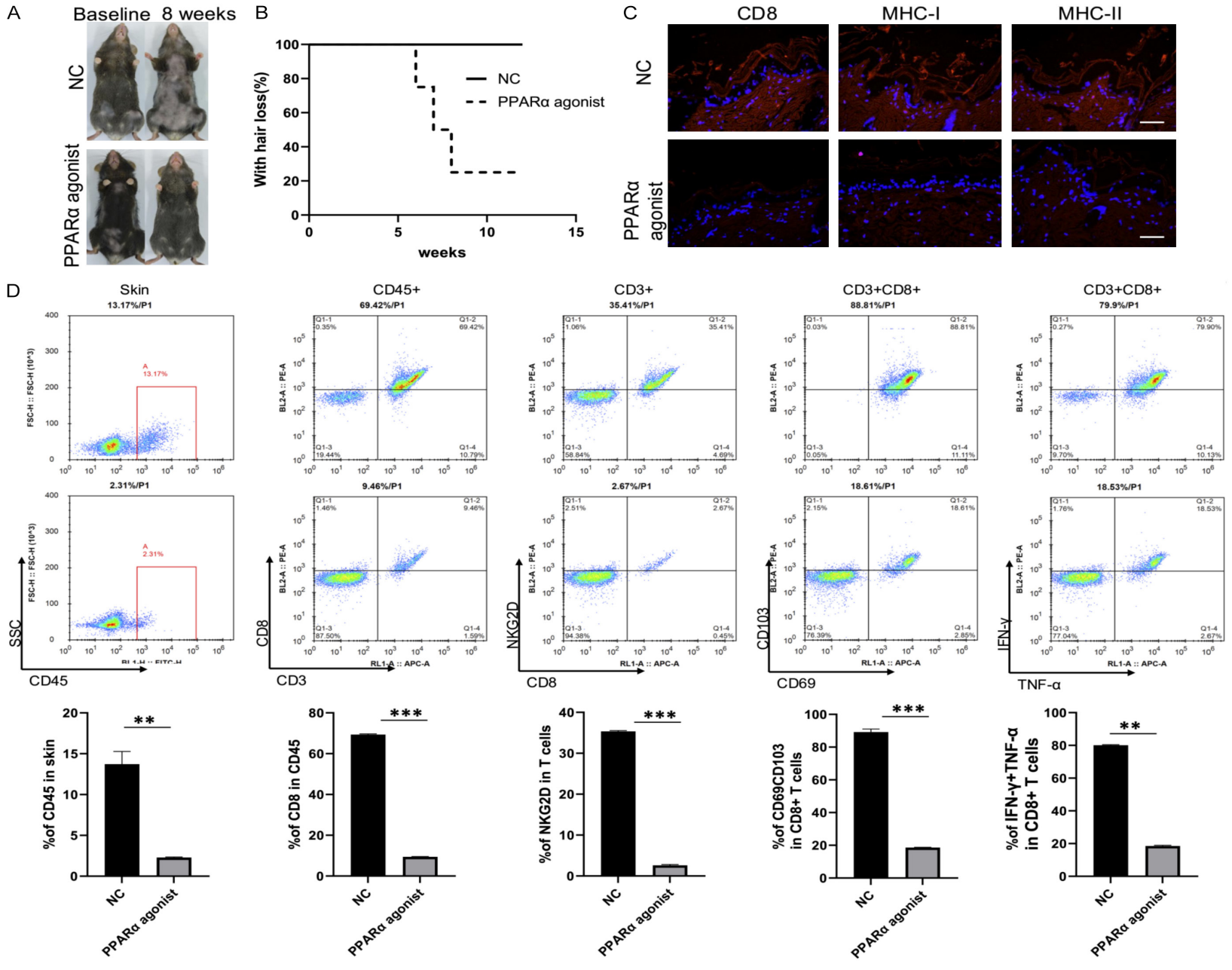
A
Baseline
8 weeks
NC
PPARα agonist
B
With hair loss(%)
weeks
NC
PPARα agonist
C
CD8
MHC-I
MHC-II
NC
PPARα agonist
D
Skin
CD45+
CD3+
CD3+CD8+
CD3+CD8+
13.17%/P1
69.42%/P1
35.41%/P1
88.81%/P1
79.9%/P1
2.31%/P1
9.46%/P1
2.67%/P1
18.61%/P1
18.53%/P1
SSC
CD45
CD8
CD3
NKG2D
CD8
CD103
CD69
IFN-γ
TNF-α
%of CD45 in skin
%of CD8 in CD45
%of NKG2D in T cells
%of CD69CD103 in CD8+ T cells
%of IFN-γ+TNF-α in CD8+ T cells
NC
PPARα agonist

Figure 4. PPARα agonist prevents the onset of AA model in T-cell receptor retrotransposon mice. A, B. Representative images and incidence of AA pathogenesis of PPARα agonist-treated and control B6 RAG1$^{-/-}$ receptor mice. C. Representative images of immunofluorescence staining of CD8, MHC I and MHC II. D. Representative flow charts and percentage summary plots of immune cells infiltrated in the skin of mice from different treatment groups, CD45+ leukocytes, CD44+CD62L-CD8+ T cells, NKG2D+CD8+ T cells, and IFN-γ+CD8+ T cells (from left to right). NC, negative control. AA, Alopecia areata. Scale bar, 50 μm. ***P*<0.01, ****P*<0.001 (one-way ANOVA).

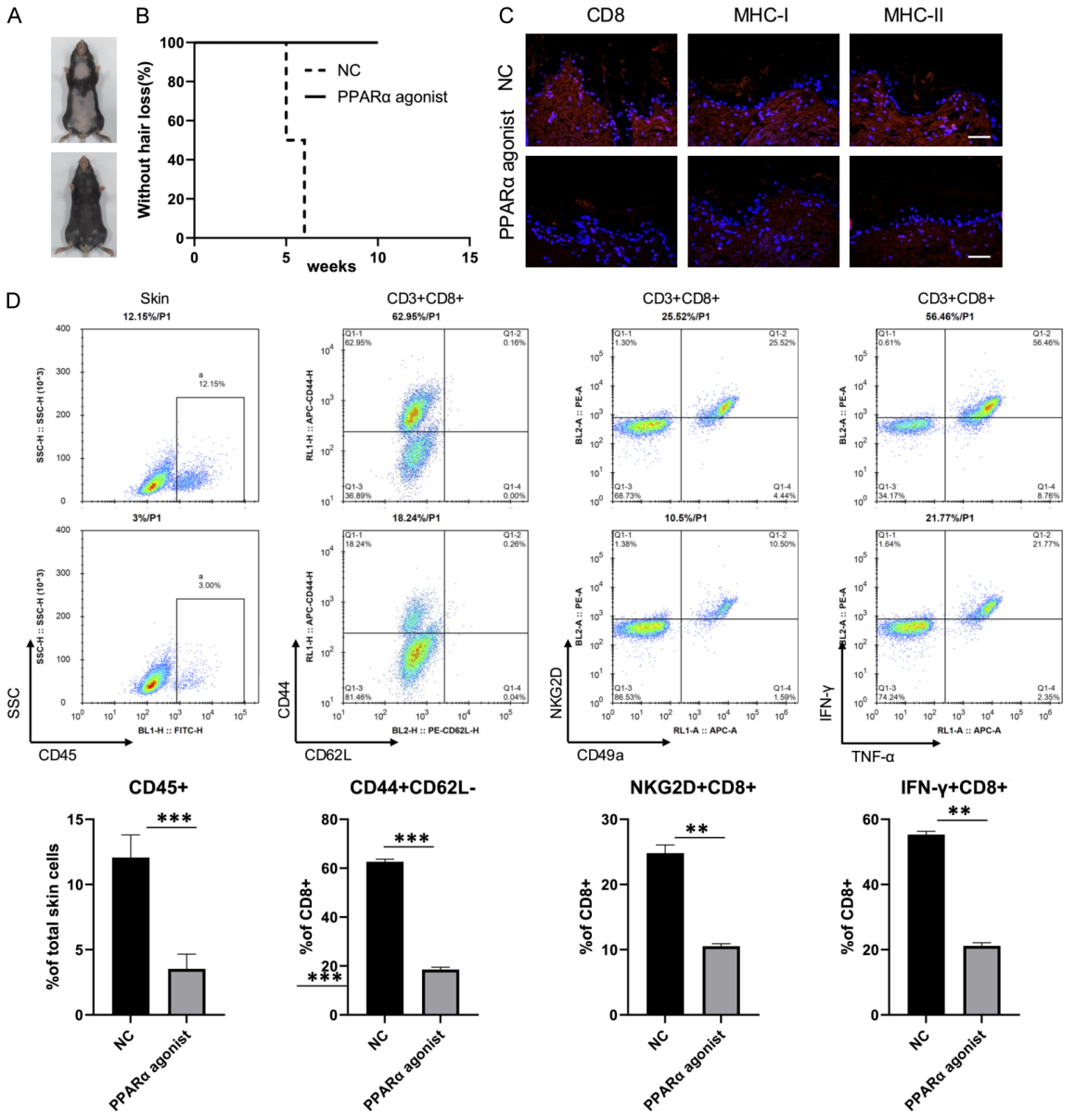

Figure 5. PPARα agonist reverses early AA in C3H/HeJ mice. Different treatment options were given to C3H/HeJ mice with early-onset AA in groups after 5 weeks following AA skin grafting. A. Representative images of PPARα agonist-treated as well as control-treated mice. B. Hair regeneration curves between the two groups. **P<0.01 (time series test). C. Images of anti-CD8, anti-MHC-I and anti-MHC-II immunofluorescence staining of skin sections from both groups. D. Flow cytometric profiles of inflammation-associated immune cell populations infiltrated in the skin and summary plots of different percentages of immune cells. NC, negative control. AA, Alopecia areata. Scale bar, 50 μm. ***P*<0.01, ****P*<0.001 (unpaired Student's t-test).

skin diseases such as atopic dermatitis, psoriasis, and others, yielding favorable clinical outcomes. Among these, targeted therapies, particularly those inhibiting the JAK-STAT signaling

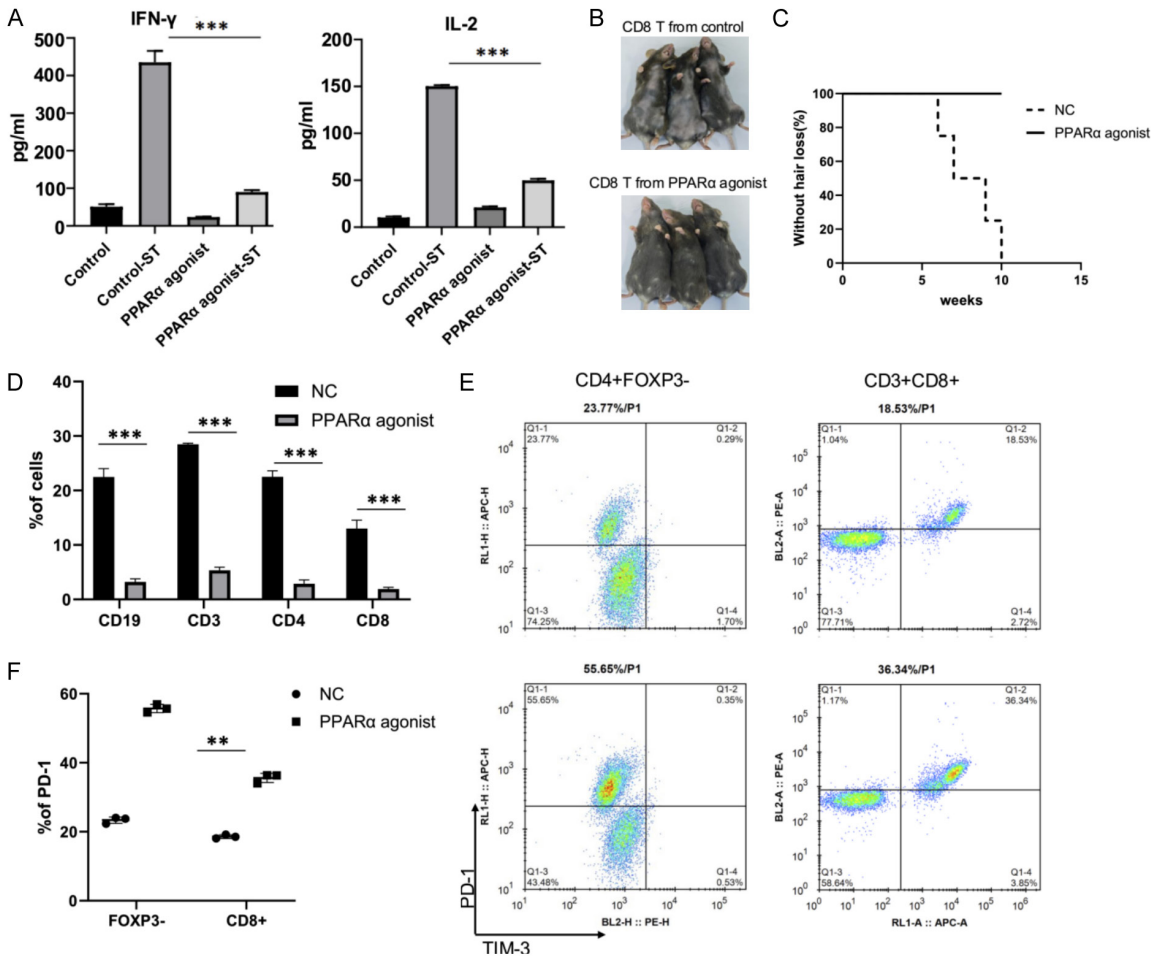

Figure 6. PPARα agonists inhibit the function of effector T cells. A. Expression of cytokines IFN-γ and IL-2 produced by T cells in SDLN stimulated (ST) with anti-CD3/CD28 for 48 hours. B, C. Changes in hair growth after transfer of activated CD8+ T cells from C3H/HeJ mice treated with both PPARα agonist and control treatment groups to normal C3H/HeJ mice. D. Total number of immune cell subsets within the SDLN of PPARα agonist and control mice. E, F. Representative flow cytometry plots and expression frequencies of PD-1+ T cells from different treatment groups. $^{**}P<0.01$, $^{***}P<0.001$.

pathway, have emerged as a valuable approach for treating AA. JAK inhibitors, a novel class of immunomodulators, have demonstrated broad applicability in managing inflammatory and autoimmune skin conditions, including psoriasis, vitiligo, atopic dermatitis, and AA. Notably, studies have highlighted the efficacy of JAK inhibitors, such as tofacitinib, ruxolitinib, and baricitinib, in AA, offering promising opportunities for developing new small-molecule targeted therapies [29, 30].

PPARs are a group of nuclear hormone receptors comprising three subtypes: PPARα, PPARβ/δ, and PPARγ, all of which are expressed in the skin [31]. Among them, PPARα, predominantly expressed in the liver and brown adipose tissue, was the first to be identified. It plays a pivotal role in regulating metabolism, particularly in maintaining energy and glucolipid homeostasis. Recent studies have reported its significant expression in immune cells, such as monocytes/macrophages, suggesting a regulatory role in immune and inflammatory responses [32]. While PPARα is also present in the skin and hair follicles, its precise physiological functions remain unclear. Conflicting findings from in vivo and ex vivo studies regarding its effects on hair growth further necessitate detailed investigation [33]. Considering the biological roles of PPARs in skin, PPAR agonists or inhibitors may hold potential as therapeutic agents for various skin diseases. However, the underlying signaling pathways by which PPARs regulate

skin structure and function remain poorly understood. Further research is required to develop novel activators targeting PPARα for precise therapeutic applications.

Our study underscores the critical role of the PPARα signaling pathway in AA. We observed marked upregulation of PPARα in the affected skin of both humans and mice with AA. Pharmacological inhibition of the PPARα signaling pathway accelerated AA progression, while PPARα agonists exhibited multiple therapeutic effects: early reversal of AA in C3H/HeJ mice, prevention of AA in a skin graft model, and reversal of pathogenesis in T-cell receptor transgenic AA mice. Immunoassays revealed that these effects were largely mediated through the suppression of desmoplastic T effector cell activity. While significant progress has been made in understanding the pathogenesis of AA and developing targeted therapies, the long-term safety, tolerability, and real-world applicability of these novel molecules warrant further investigation. In conclusion, our findings highlight the therapeutic potential of the PPARα signaling pathway and PPARα agonists in the treatment of AA.

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Disclosure of conflict of interest

None.

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